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10/621,428	07/16/2003	Dieter Heindl	022101-003900US	8931

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TOWNSEND AND TOWNSEND AND CREW, LLP
2 EMBARCADERO CENTER, 8TH FLOOR
SAN FRANCISCO, CA 94111

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,428	HEINDL ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *18-23,32,34,35 and 37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *35,37 and 44* is/are allowed.

6)☒ Claim(s) *18-23,32,34 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *5/2007*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on June 7, 2007 has been entered. The claims pending in this application are claims 18-23, 32, 34, 35, and 37-44. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on June 7, 2007.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 18, 20, 22, 23, and 43 are rejected under 35 U.S.C. 102(e) or (a) as being anticipated by Wilson *et al.,* (US Patent No. 6,355,435 B1, filed on September 6, 2000 and published on March 12, 2002).

Regarding claim 18, Wilson *et al.,* teach a solution (ie., the PCR reaction mixture in claim 6 or the allelic discrimination reaction in column 14) comprising a plurality of fluorescence resonance energy transfer (FRET) hybridization probes comprising first

oligonucleotide (ie.,TAQ2 comprising SEQ ID NO:6) carrying a FRET donor entity (ie., FAM) and at least one second entity (ie., the quencher or TAMRA), said second entity being a compound which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and a second oligonucleotide (ie., TAQ3 comprising SEQ ID NO:7) carrying a FRET acceptor entity (ie., the quencher or TAMRA), wherein the FRET donor entity (ie. FAM on TAQ2) of the first oligonucleotide and the FRET acceptor entity (ie., the quencher or TAMRA on TAQ3) of the second oligonucleotide are a FRET pair, wherein the FRET acceptor entity (ie., the quencher or TAMRA on TAQ3) and the FRET donor entity (ie. FAM on TAQ2) of the FRET pair are on different oligonucleotides, wherein the first and second oligonucleotides are single-stranded over their full length before hybridization as recited in claim 18 (see columns 13 and 14, claim 6 in columns 38 and 39, and Figures 1 and 2).

Regarding claim 20, Wilson *et al.,* teach a solution (ie., the PCR reaction mixture in claim 6) comprising 3 oligonucleotides, the solution comprising a first oligonucleotide (ie., TAQ2 in Figures 3A and 3B as a forward primer) and a second oligonucleotide (ie., JL239 in Figures 3A and 3B or SEQ ID NO:4 in column 11 and claim 6 as a reverse primer) capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction, further characterized in that said first oligonucleotide (ie., TAQ2) and a third oligonucleotide (ie., TAQ3) are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity (ie. FAM on TAQ2) and a FRET acceptor entity (ie., the quencher or TAMRA on TAQ3) wherein the oligonucleotide carrying the FRET donor entity further carries at least one second entity (ie., the quencher or TAMRA on TAQ2), said second entity being a compound which is capable of quenching fluorescence of said FRET donor entity;

and wherein the FRET acceptor entity and the FRET donor entity of the FRET pair are on different oligonucleotides (see columns 11-14, claim 6 in columns 38 and 39, and Figures 1, 2, 3A, and 3B).

Regarding claim 22, Wilson *et al.*, teach further comprising a nucleic acid sample (ie., the sample containing nucleic acids) (see claim 6 in columns 38 and 39).

Regarding claim 23, Wilson *et al.*, teach further comprising at least one other component selected from a group consisting of a nucleic acid amplification primer, a template dependent nucleic acid polymerase, at least one deoxynucleoside triphosphate and a buffer for template dependent nucleic acid amplification reaction (see claim 6 in columns 38 and 39).

Regarding claim 43, Wilson *et al.*, teach a kit comprising the solution of claim 18 (see claim 12 in column 40).

Therefore, Wilson *et al.*, teach all limitations recited in claims 18, 20, 22, 23, and 43.

4. Claims 18-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathies *et al.*, (US Patent No. 6,028,190, published on February 22, 2000).

Regarding claim 18, Mathies *et al.*, teach a solution (ie., the mixture comprising amplified fragments, F10F primer, F14F primer, F2R primer and F6R primer before electrophoresis, see column 21, first paragraph and Figures 17A and 22) comprising a plurality of fluorescence resonance energy transfer (FRET) hybridization probes comprising first oligonucleotide (ie., F2R primer) carrying a FRET donor entity (ie., FAM) and at least one second entity (ie., ROX), said second entity being a compound which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and a second oligonucleotide

(ie., F6R primer) carrying a FRET acceptor entity (ie., ROX), wherein the FRET donor entity (ie. FAM on F2R primer) of the first oligonucleotide and the FRET acceptor entity (ie., ROX on F6R primer) of the second oligonucleotide are a FRET pair, wherein the FRET acceptor entity (ie., ROX on F6R primer) and the FRET donor entity (ie., FAM on F2R primer) of the FRET pair are on different oligonucleotides, wherein the first and second oligonucleotides are single-stranded over their full length before hybridization as recited in claim 18 (see column 4, second paragraph, column 21, first paragraph and Figures 17A and 22).

Regarding claim 20, Mathies *et al.,* teach a solution (ie., the mixture comprising amplified fragments, F10F primer, F14F primer, F2R primer and F6R primer before electrophoresis, see column 21, first paragraph and Figures 17A and 22) comprising 3 oligonucleotides, the solution comprising a first oligonucleotide (ie., F2R primer) and a second oligonucleotide (ie.,F14F primer) capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction, further characterized in that said first oligonucleotide (ie., F2R primer) and a third oligonucleotide (ie., F6R primer) are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity (ie. FAM on F2R primer) and a FRET acceptor entity (ie., ROX on F6R primer) wherein the oligonucleotide carrying the FRET donor entity further carries at least one second entity (ie., ROX on F2R primer), said second entity being a compound which is capable of quenching fluorescence of said FRET donor entity; and wherein the FRET acceptor entity and the FRET donor entity of the FRET pair are on different oligonucleotides (see column 4, second paragraph, column 21, first paragraph and Figures 17A and 22).

Regarding claims 19 and 21, since Mathies *et al.*, teach that the FRET donor entity (ie., FAM) and the second entity (ie., ROX) are carried on adjacent nucleotides of the first oligonucleotide (ie., F2R primer) as recited in claims 19 and 21 (see Figure 22).

Regarding claim 22, Mathies *et al.*, teach further comprising a nucleic acid sample (ie., the sample containing THO1 target) (see column 4, second paragraph).

Regarding claim 23, Mathies *et al.*, teach further comprising at least one other component selected from a group consisting of a nucleic acid amplification primer, a template dependent nucleic acid polymerase (ie., Taq DNA polymerase), at least one deoxynucleoside triphosphate and a buffer for template dependent nucleic acid amplification reaction (see column 18, second paragraph and column 4, second paragraph).

Therefore, Mathies *et al.*, teach all limitations recited in claims 18-23.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 32, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson *et al.*, as applied to claims 18, 20, 22, 23, and 43 above, and further in view of Wittwer *et al.*, (US Patent No. 6,635,427, priority date: August 11, 2000).

The teachings of Wilson *et al.*, have been summarized previously, *supra.*

Regarding claim 32, in view of claims 18 and 32 and above rejection under 35 U.S.C 102, Wilson *et al.*, teach all limitations of claim 32 except a nitroindole moiety.

Regarding claims 38 and 39, since clams 22 and 38 are identical while claims 23 and 39 are identical, Wilson *et al.*, teach claims 38 and 39.

Wittwer *et al.*, teach a single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity (see column 43, claims 1 and 2).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a solution comprising a first single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity in view of the patents of Wilson *et al.*, and Wittwer *et al.*. One having ordinary skill in the art would have been motivated to do so because Wittwer *et al.*, have taught a first single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity and the simple substitution of one kind of fluorescent quencher (ie., ROX taught by Wilson *et al.*,) from another kind of fluorescent quencher (ie., a nitroindole moiety taught by Wittwer *et al.*,) during the

process of making the first single-stranded oligonucleotide recited in claim 32, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since both ROX taught by Wilson *et al.*, and the nitroindole moiety taught by Wittwer *et al.*, are used for the same purpose (ie., working as a fluorescent quencher).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

7. Claims 32, 34, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathies *et al.*, as applied to claims 18-23 above, and further in view of Frutos *et al.*, (US Patent No. 6,579,680 B2, priority date: February 28, 2001).

The teachings of Mathies *et al.*, have been summarized previously, *supra.*

Regarding claim 32, in view of claims 18 and 32 and above rejection under 35 U.S.C 102, Mathies *et al.*, teach all limitations of claim 32 except a nitroindole moiety.

Regarding claims 38 and 39, since clams 19, 22, and 23 are identical to claims 34, 38, and 39, Mathies *et al.*, teach claims 34, 38 and 39.

Frutos *et al.*, teach a single-stranded oligonucleotide carrying a fluorescent dye and a nitroindole moiety capable of quenching fluorescence dye (see column 7).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a solution comprising a first single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity in view of the patents of Mathies *et al.*, and Frutos *et al.*. One having ordinary skill in the art would have been motivated to do so because Frutos *et al.*, have taught a single-stranded oligonucleotide carrying a fluorescent dye and a nitroindole moiety capable of quenching fluorescence dye (see column 7) and the simple substitution of one kind of fluorescent quencher (ie., ROX taught by Mathies *et al.*,) from another kind of fluorescent quencher (ie., a nitroindole moiety taught Frutos *et al.*,) during the process of making the first single-stranded oligonucleotide recited in claim 32, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

8. Claims 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson *et al.*, as applied to claims 18, 20, 22, 23 and 43 above, and further in view of Segev (US Patent No. 5,437,977, published on August 1, 1995).

The teachings of Wilson *et al.*, have been summarized previously, *supra.*

Regarding claims 40 and 41, in view of claims 18, 20, 40, and 41, and above rejection under 35 U.S.C 102, Wilson *et al.*, teach all limitations of claims 40 and 41 except a solid support comprising a plurality of FRET hybridization probes as recited in claim 40 and a solid support comprising 3 olgonucleotides as recited in claim 41.

Segev teaches that immobilizing the target nucleic acid molecule occurs before hybridizing the primary probe to the target nucleic acid molecule. The advantage of immobilizing the target nucleic acid molecule is that the unhybridized labeled molecules is separated from the immobilized complex prior to detection, thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a support comprising a plurality of FRET hybridization probes recited in claim 40 and a support comprising 3 olgonucleotides as recited in claim 41 by immobilizing the nucleic acid sample taught by Wilson *et al.*, to a support before the PCR reaction in order to form a support comprising the plurality of FRET hybridization probes and the nucleic acid sample, and a support comprising 3 olgonucleotides and the nucleic acid sample in view of patents of Wilson *et al.*, and Segev. One having ordinary skill in the art has been motivated to do so because Segev suggests that immobilizing the target nucleic acid molecule before hybridization assay would enhance separation of unhybridized molecules from

the immobilized complex prior to detection and thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to make a support comprising a plurality of FRET hybridization probes as recited in claim 40 and a solid support comprising 3 olgonucleotides as recited in claim 41.

9. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al., in view of Wittwer et al., as applied to claims 18, 20, 22, 23, 32, 38, 39, and 43 above, and further in view of Segev.

The teachings of Wilson *et al.*, and Wittwer *et al.*, have been summarized previously, *supra.*

In view of claims 32 and 42, since a plurality of FRET hybridization probes recited in claims 32 and 42 are identical, Wilson *et al.*, in view of Wittwer *et al.*, teach a plurality of FRET hybridization probes recited in claim 42.

Wilson *et al.*, and Wittwer *et al.*, do not disclose a solid support comprising a plurality of FRET hybridization probes as recited in claim 42.

Segev teaches that immobilizing the target nucleic acid molecule occurs before hybridizing the primary probe to the target nucleic acid molecule. The advantage of immobilizing the target nucleic acid molecule is that the unhybridized labeled molecules is separated from the immobilized complex prior to detection, thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art

at the time the invention was made to have made a support comprising a plurality of FRET hybridization probes recited in claim 42 by immobilizing the nucleic acid sample taught by Wilson *et al.*, to a support before the PCR reaction in order to form a support comprising the plurality of FRET hybridization probes and the nucleic acid sample in view of patents of Wilson *et al.*, and Wittwer *et al.*, and Segev. One having ordinary skill in the art has been motivated to do so because Segev suggests that immobilizing the target nucleic acid molecule before hybridization assay would enhance separation of unhybridized molecules from the immobilized complex prior to detection and thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to make a support comprising a plurality of FRET hybridization probes as recited in claim 42.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Claims 35, 37, and 44 are allowed over prior art.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

July 24, 2007

FRANK LU
PRIMARY EXAMINER